

## **REMARKS**

Claims 1 to 43 are pending in this application. Claims 9, 10 and 18 to 43 are withdrawn from consideration as directed to a non-elected invention. Claims 3-7 are cancelled herein without prejudice. The Applicant reserves the right to file one or more continuing applications containing these canceled claims. Claims 1 and 2 are amended herein for clarity to more particularly define the elected invention. Claim 14 has been modified to correct a minor irregularity found by the Applicant. Claim 15 has been amended to conform with the wording of new claim 1. Claim 43 (and claim 24) has been amended according to the Examiner's suggestion. Support for these amendments is found in the language of the original claims and throughout the specification as set forth herein. In particular, amended claim 1 finds support in canceled claim 3. It is believed that no new matter is added by these amendments. The Applicant respectfully requests entry of these amendments and reconsideration and allowance of the pending claims.

### **I. Objection to the specification**

As requested by the Examiner, claim 43 has been amended to incorporate the SEQ ID numbers for the claimed sequences. The Applicant has similarly amended claim 24.

### **II. Objection to the claims**

As requested by the Examiner, the phrase "when present into a suitable host" in claim 1 has been replaced by the phrase - -when present in a suitable host- -.

### **III. Rejections under 35 USC 112, first paragraph**

The Applicant has taken good note of the rejection of claims 1 to 8 and 11 to 17 under 35 USC 112, first paragraph as:

- 1) allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention; and

- 2) as allegedly lacking enablement for a signal trap screening method employing any viral genome having any desired features using any suitable host wherein any suppressive condition is used to mark the success or failure of the screening method.

As the Examiner may appreciate, claim 1 has been amended to better define the elected invention. More specifically, new claim 1 now clearly defines a signal trap method employing a viral genome encoding a dysfunctional signal peptide. This new claim finds adequate support throughout the specification, and especially in claim 3 and in Example 1. It is thus clear that the Applicant was in possession of the claimed method at the time of filing.

Furthermore, the Applicant submits that the present application satisfies the enablement requirement because there is sufficient disclosure (see Example I) to teach those skilled in the art how to make and use the invention as claimed in new claim 1 and its dependent claims.

In view of the above, the Examiner is kindly requested to withdraw his rejections.

#### **IV. Rejections under 35 USC 112, second paragraph**

The Applicant has taken good note of the rejection of claim 1 and its dependent claims under 35 USC 112, second paragraph, as allegedly being indefinite for the use of the term “packaging”, on the basis that the Applicant has allegedly incorrectly expanded the definition of such a term to include not only the incorporation of genetic material into a virus capsid but also to include the release of said genetic material out of the virus capsid.

For a purpose of clarity, the term “packaging” has been deleted from claim 1 and replaced by the term - -producing- -. The objection is thus believed to be traversed. Support for this amendment can be found throughout the specification as filed, e.g., see page 11, line 29 to page 12, line 2; page 13, lines 14-21; etc.

The Applicant has also taken good note of the rejection of claim 5 under 35 USC 112, second paragraph, as allegedly being indefinite for the recitation of the expression “fetter proteins”. In order to expedite prosecution of the pending claims to issuance, claim 5 is cancelled herein without prejudice.

## **V. Rejections under 35 USC 102 and 35 USC 103**

The Examiner has rejected claims 1, 2, 11, 12, 15 and 16 presently on file as lacking novelty in view of Parks et al. (Proc. Natl. Acad. Sci. U.S.A, 1996, vol. 93, pp.13565-13570).

The Examiner has also rejected claims 1 to 6, 11, 12 and 15 to 17 presently on file as lacking novelty in view of Zhang et al. (US Patent No. 6,150,098).

The subject matter of claims 1, 2, 8 and 11 to 16 has been rejected for being obvious in light of combinations of Parks et al. and Huang et al. (US Patent 5,217,879, June 1993) or Zhang et al. and Huang et al.

The Applicant respectfully submits that the subject matter of new claims 1, 2, 4, 8 and 11-17 is new and not obvious for the following reasons.

First of all, the Applicant wishes to remind the Examiner that the present invention relates to methods to screen libraries of nucleic acids in order to specifically retrieve those encoding given functions. Nucleic acids are incorporated in a viral genome that has been engineered such that it cannot be released as part of an infectious viral particle in the cell culture medium unless the function expressed by the inserted nucleic acid can restore the release of infectious viral particles. In other words, screening is performed through genetic complementation and retrieval is achieved through collection of infectious viral particles in the culture medium.

Expression screening in mammalian cells is a well-established methodology. It should be emphasized that the present invention, while comprising known steps of this methodology, i.e., expression of heterologous nucleic acids from engineered viral genomes, relates mainly to methods to retrieve particular nucleic acids after expression screening in a mammalian host. In other words, while it may be obvious from prior art that engineered viral genomes can be used as gene delivery tools in an expression screening strategy, it is certainly not obvious that they can be simultaneously used as gene retrieval tools. This dual property of an engineered viral genome that expresses a nucleic acid AND releases it in a viral particle if it encodes a given function, forms the basis of the present invention. As the Examiner will appreciate, new claim 1 refers to viral genomes engineered in such a way as to combine these properties. More specifically, new claim 1 refers to a method designed to screen for nucleic acids encoding signal peptides according to a

signal trap strategy. A viral genome is rendered defective for particle formation/release by removing the sequence encoding the signal peptide of a viral protein such as an essential envelope protein (the "reporter" using the signal trap terminology). Heterologous nucleic acids are inserted upstream of this reporter. After transfection of a library of recombinant viral genomes in mammalian cells (not infection of cells by a library of recombinant viral particles), viral particles will only be produced from cells expressing an heterologous nucleic acid that encodes a signal peptide able to restore secretion of the envelope protein. These viral particles comprise copies of the viral genome and hence, copies of the heterologous nucleic acid inserted therein. This presently claimed method illustrates that desired viral genomes should possess both the ability to express heterologous nucleic acids AND the potential to retrieve those encoding specific functions.

Parks et al. discloses methods for using modified adenoviruses as vectors for the delivery of foreign genes in mammalian cells. As the Examiner will note, it does not teach in anyway how to use such vectors as selective gene retrieval tools in an expression screening setting. More specifically, it does not disclose how to conditionally link expression of a "foreign gene" with relief of a "suppressive condition". As explained above, the present invention relates to screening methods based on such a link. As the Examiner may appreciate, the present invention differs from helper-dependent viral particle production systems, such as the one described by Parks et al., in another important way. Indeed, and as stated by the Examiner (line 11, page 13 of his report), a "helper" viral genome complements *in trans* a second defective viral genome, usually harboring a foreign gene. Complementation in the present claimed method involves a single molecule and works *in cis*, i.e. the "suppressive condition" is not overcome with the help of a helper virus but with the help of the "foreign gene".

Zhang et al. discloses methods based on a signal trap strategy. However, contrary to what is assumed by the Examiner and as stated on page 14, lines 2-3 of his report, Zhang et al. does not teach how to use viral vectors to screen for novel secreted proteins. Indeed, Zhang et al. discloses methods using plasmid-based vectors. On columns 5-6, Zhang et al. describes regulatory sequences derived from viral genomes (e.g. long terminal repeats of retroviruses, SV40 promoter) and incorporated in plasmid-based vectors for expression in mammalian cells. These viral elements are widely used in vector construction and do not constitute defective viral genomes in

the accepted sense. Furthermore, the "suppressive" condition developed by Zhang et al. (i.e. nutrient requirement) affects growth of the transfected cells. No link between nutrient requirement and viral packaging is made by Zhang et al. In fact, these inventors do not mention viral packaging at all in the context of gene selection or retrieval.

In view of the above, the Applicant submits that new claim 1 and its dependent claims are novel in view of either Parks et al. or Zhang et al.

Huang et al. discloses methods for expressing nucleic acids in cells, by using a recombinant Sindbis virus genome. Contrary to Huang et al. the present invention rather relates to methods for screening nucleic acids in cells.


It is believed clear from the above discussion that the obviousness rejection is based on the combination of Parks et al. and Huang et al. or Zhang et al. and Huang et al. seeking to reconstruct the Applicant's invention. It is submitted, however, that this is an improper rejection under 35 USC 103 because the references themselves do not suggest the teaching relied on by the Examiner.

The Applicant thus submits that the combined teachings of Huang et al. and Parks et al. or Zhang et al., fail to make out a proper *prima facie* case of obviousness.

For the foregoing reasons, the Applicant believes that all the pending rejections have been adequately addressed and that the claims presented herein are in condition for allowance.

Respectfully submitted,

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